UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,647	07/17/2001	Ramachandran Murali	UPN-3963	3796

23377 7590 05/19/2009

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
CLOW, LORI A	
ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
05/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/720,647	MURALI ET AL.	
	Examiner	Art Unit	
	LORI A. CLOW	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-26 and 28-32* is/are pending in the application.

4a) Of the above claim(s) *9-24 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8, 25, 26, and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, filed 9 February 2009, has been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 6-26, and 28-32 are currently pending. Claims 1-5 and 27 have been cancelled. Claims 9-24 and claim 32 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 16 August 2004. Claims 6-8, 25, 26 and 28-31 are examined herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6-8, 25, 26, and 28-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over the program user's guide for DOCK (Version 4.0; Regents of the University of California (1998); pages 1-120 Edited by Todd Ewing; PTO form 1449 reference), as further evidenced by Kuntz (Science (1992) vol. 257, pages 1078-1082; PTO form 1449 reference) in view of Takasaki et al. (Nature Biotechnology (1997) Vol. 15: pages 1266-1270; PTO form 1449), in further view of Tang et al. (Chemistry and Biology (1997) Vol. 4, pages 453-459; PTO form 1449 reference), for the reasons set forth in the previous Office Action and re-iterated below. This rejection is necessitated in-part by claim amendment

Instant claim 26 is drawn to a method of identifying a *small molecule* compound that is an allosteric modulator of an intermolecular interaction at a functionally critical site of a target protein and a modifier including identifying an allosteric cavity on a target that is within about *15 to 20 angstroms* of the critical site; calculation of cavity dimensions and mapping chemical or electrostatic properties; using dimension to identify compounds that have a functional group that can accommodate the cavity; and assay compounds in vitro.

In regard to claims 6-8, and 25, 26, and 28-31, the DOCK program User's Guide teaches a program in which favorable orientations of a ligand in a receptor may be elucidated. A potential site of interest on the receptor is identified, often the active site. Points are identified within the site where ligands may be located. Sphere centers are identified by generating a set of overlapping spheres to fill the site. The sphere centers capture shape characteristics of the active site (or site of interest). Distances are calculated and shape scoring functions utilized (or binding energy functions) for ligand orientation (page 11, introduction). Further, critical points may be identified in which multiple critical sites are identified (page 21, user's guide). Similarity screens may also be performed to identify all molecules in a database which may be similar to a particular molecule of interest that has been elucidated (page 45, user's guide). As further elucidated by Kuntz (1992) the DOCK program characterizes the entire surface of a molecule, seeking grooves and invaginations in the surface that form target sites. Typically, sites that are found by the program include active regions of enzymes, recognition and allosteric features (page 1080, column 1). The DOCK program also measures distances, making it obvious to measure cavities within 15 to 20 angstroms of a critical site.

DOCK does not specifically teach identification of compound that modulates intermolecular interaction between what is called a functionally critical site of a target protein and a modifier or an allosteric modulation. However, Takasaki et al. teach structure based design and characterization of an inhibitor of TNFα binding to its receptor. Takasaki teaches the notion of three critical binding sites of the TNF-receptor to which TNFα binds based upon crystal structures of receptor complexes (page 1266, column 2). Small molecule peptidomimetics were designed that were antagonists. In vitro assays were performed for

verification (page 1267, column 2). Takasaki et al. were able to demonstrate that that one site in particular, WP9, was critical to antagonize TNFα activity (page 1269, column 1). Further mutation studies and antigenic epitope mapping were used to assign functions to particular regions of the TNFα molecule. Studies indicated that a contact site proximal to the transmembrane is critical.

Neither DOCK nor Takasaki et al. specifically teach identification of an allosteric cavity, however, Tang et al. teach the allosteric regulation of protein enzymes at allosteric binding sites, located apart from the active site of the protein that can recognize effector molecules (page 453, column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used DOCK for cavity mapping of in the design of peptidomimetic inhibitors for allosteric sites, as was done by Takasaki for critical site such as WP9. One would have been motivated to do so because all the claimed elements were known in the prior art, such as docking (the DOCK program), the crystal structure of TNFα, needed for docking calculations, and the concept of allosteric cavities, as taught by Tang et al., that specifically recognize effector molecules. Further, one of skill in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention.

Response to Applicant's Arguments

1. Applicant argues that the DOCK User's Guide completely fails to mention any allosteric cavity or provide a suggestion as to how one might go about identifying a cavity that would modulate interactions at a functionally critical site.

This is not persuasive. As is sated above in reference to Kuntz, the DOCK program is capable of identifying allosteric regions. Further, it is the combination of references that is relied upon to teach identification of compounds that could regulate such a site. As seen in Takasaki et al. small molecules are designed to interact with three critical binding sites of the TNF-receptor to which TNFα binds based upon crystal structures of receptor complexes (page 1266, column 2). Takasaki et al. were able to demonstrate that that one site in particular, WP9, was critical to antagonize TNFα activity (page 1269, column 1). Further mutation studies and antigenic epitope mapping were used to assign functions to particular regions of the TNFα molecule. Studies indicated that a contact site proximal to the transmembrane is critical. Tang et al. are relied upon to teach that alternative sites to critical sites are allosteric sites and that these sites can recognize effector molecules. Furthermore, in the instant specification uses such programs as DOCK to determine functional cavities (page 12, lines 4-14). Therefore, it would have been obvious to use DOCK to identify sites for allosteric modification by small molecules.

2. Applicant argues that the Takasaki reference does not teach or suggest identifying an allosteric site on the receptor. Takasaki is concerned with identification of one of the critical sites, WP9, on the TNF receptor. As stated above, it is the combination of references that are relied upon to teach the instant claimed methods. Applicant is reminded that one cannot show

nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

3. Applicant argues that Tang has nothing to do with the methods of the present invention and that Tang is concerned with ribosomal constructs and not with identification of small molecules. Again, it is the combination of references that is relied upon to teach the instant claimed limitations. Further, Tang teaches how small molecules (small effector molecules) can be tightly designed to interact with allosteric binding sites and prevent ligand (RNA)/ receptor critical site (ribozyme) interactions. Therefore, Tang is relevant to the instant claimed methods. There is nothing in the claim language to exclude ribosomal constructs or to exclude RNA or DNA as a small molecule.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

May 19, 2009
/Lori A. Clow, Ph.D./
Primary Patent Examiner
Art Unit 1631